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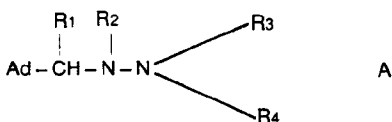
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54 **Methyladamantyl hydrazines, their preparation and pharmaceutical compositions containing them.**

57 The invention provides novel 1- or 2-adamantylmethyl hydrazines of the general formula A



Several methods of preparation of the new compounds are described.

The novel compounds according to the invention possess valuable antifungal (human and plant), antiviral, antiprotozoal and antimicrobial properties.

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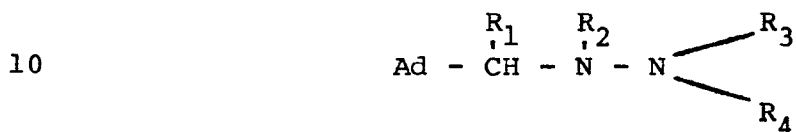
In this formula Ad is 1- or 2-adamantyl, R<sub>1</sub> and R<sub>2</sub> are the same or different and are each hydrogen or a lower unsubstituted or substituted alkyl group of 1-4 carbon atoms; R<sub>3</sub> and R<sub>4</sub> are the same or different and are each hydrogen, an unsubstituted or substituted radical being a lower alkyl group of 1-4 carbon atoms, a lower alkanolic acid radical of 2-4 carbon atoms or a lower alkyl ester thereof, adamantyl, aryl, aralkyl in which the alkyl moiety has 1-4 carbon atoms or an unsubstituted or substituted heterocyclic radical of aromatic character; or R<sub>3</sub> and R<sub>4</sub> together with the nitrogen atom to which they are attached form a cyclic radical of non-aromatic character.

The invention further provides pharmaceutically acceptable acid addition salts of the above compounds.

1 Methyladamantyl hydrazines, their preparation and  
pharmaceutical compositions containing them

5 The present invention relates to novel  
adamant-1- or -2-ylmethyl hydrazines, to pharmaceutic-  
ally acceptable acid addition salts thereof and to  
methods of preparing the novel compounds and their  
salts.

Specifically the invention provides 1- or  
2-adamantylmethyl hydrazines of the general formula A



wherein Ad is 1- or 2-adamantyl, R<sub>1</sub> and R<sub>2</sub> are the same  
or different and are each hydrogen or a lower  
unsubstituted or substituted alkyl group of 1-4  
carbon atoms; R<sub>3</sub> and R<sub>4</sub> are the same or different and  
15 are each hydrogen, an unsubstituted or substituted  
radical being a lower alkyl group of 1-4 carbon atoms  
a lower alkanolic acid radical of 2-4 carbon atoms or a  
lower alkyl ester thereof, adamantyl, aryl, aralkyl in  
which the alkyl moiety has 1-4 carbon atoms or an  
20 unsubstituted or substituted heterocyclic radical of  
aromatic character; or R<sub>3</sub> and R<sub>4</sub> together with the  
nitrogen atom to which they are attached form a cyclic

1 radical of non-aromatic character; and pharmaceutically acceptable acid addition salts thereof.

The term "lower alkanolic acid or ester radical" refers herein to a radical which is linked  
5 to the hydrazine nitrogen atom at one of the non-carboxylic carbon atoms thereof, i.e. at a carbon atom forming part of the lower alkyl moiety of said radical.

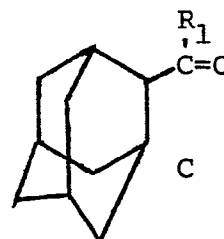
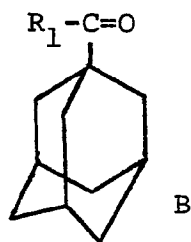
Where  $R_3$  and/or  $R_4$  is a lower alkyl ester of  
10 a lower alkanolic acid of 2-4 carbon atoms, the ester forming lower alkyl radical may, for example, be methyl, ethyl, propyl or butyl.

Examples of heterocyclic radicals of aromatic character for which either of  $R_3$  and  $R_4$  may stand are  
15 pyridinyl or quinolinyl.

Examples of cyclic radicals formed by  $R_3$ ,  $R_4$  and the nitrogen atom to which they are attached are  
piperidino, homopiperidino, pyrrolidino, morpholino, thiomorpholino, hydantoino, piperazino or heptamethylene-  
20 imino radicals all of which radicals may be substituted.

A compound of formula A in which  $R_2$  is hydrogen can be prepared in accordance with the invention by reacting a compound of either of formulae B and C:

25



- 1           13.   1-(Adamant-2'-ylmethyl)-2,2-dimethyl-  
          hydrazine and pharmaceutically acceptable acid  
          addition salts thereof.
14.   1-(Adamant-2'-ylmethyl)-2-(pyrid-2"-yl)-  
5       hydrazine and pharmaceutically acceptable acid  
          addition salts thereof.
15.   (Adamant-1'-ylmethyl)hydrazine and  
          pharmaceutically acceptable acid addition salts  
          thereof.
- 10          16. 1-(Adamant-1'-ylmethyl)-1-methylhydrazine and  
          pharmaceutically acceptable addition salts thereof.
17.   1-(Adamant-2'-ylmethyl)-1-methylhydrazine  
          and pharmaceutically acceptable acid addition salts  
          thereof.
- 15          18.   Ethyl [2-(adamant-1'-ylmethyl)C]hydrazino]-  
          acetate and pharmaceutically acceptable acid addition  
          salts thereof.
19.   [2-(Adamant-1'-ylmethyl)hydrazino]acetic  
          acid and pharmaceutically acceptable acid addition  
20       salts thereof.
20.   1,1-Dimethyl-2-(adamant-2'-ylmethyl)-  
          hydrazine and pharmaceutically acceptable acid addition  
          salts thereof.
21.   [1-(Adamant-1'-yl)ethyl]hydrazine and  
25       pharmaceutically acceptable acid addition salts thereof.
22.   1-[1'-(Adamant-1"-yl)ethyl]-2-methyl-  
          hydrazine and pharmaceutically acceptable acid addition  
          salts thereof.

1                   23.    1-[1'-(Adamant-1"-yl)ethyl]-2-(m-  
trifluoromethylphenyl)hydrazine and pharmaceutically  
acceptable acid addition salts thereof.

5                   24.    1-(Adamant-1'-ylmethyl)-2-[1"-(2"-hy-  
droxyethyl)]hydrazine and pharmaceutically acceptable  
acid addition salts thereof.

25.    1-(Adamant-1'-ylmethyl)-2-phenethyl-  
hydrazine and pharmaceutically acceptable acid  
addition salts thereof.

10                  26.    1-(Adamant-1'-ylmethyl)-2-(p-bromo-  
phenyl)hydrazine and pharmaceutically acceptable acid  
addition salts thereof.

15                  27.    1-(Adamant-1'-ylmethyl)-2-[4"-(7"-  
chloroquinolinyl)]hydrazine and pharmaceutically  
acceptable acid addition salts thereof.

28.    1-(Adamant-1'-ylmethyldamino)-2-methyl-  
pyrrolidine and pharmaceutically acceptable acid  
addition salts thereof.

20                  29.    1-(Adamant-1'-ylmethyldamino)homo-  
piperidine and pharmaceutically acceptable acid  
addition salts thereof.

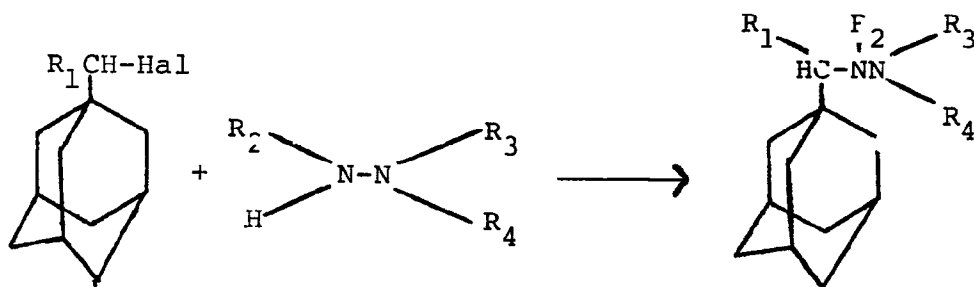
30.    1-(Adamant-1'-ylmethyldamino)hepta-  
methylenimine and pharmaceutically acceptable acid  
addition salts thereof.

25                  31.    1-(Adamant-2'-ylmethyldamino)-  
pyrrolidine and pharmaceutically acceptable acid  
addition salts thereof.

- 1 1-(Adamant-2'-ylmethylamino)piperidine  
1-(Adamant-1'-ylmethylamino)thiomorpholine  
1-(Adamant-1'-ylmethylamino)hydantoin  
1-(Adamant-1'-ylmethyl)-2-butylhydrazine

- 5 By another embodiment adamantylmethyl hydrazines of formula A are prepared by condensation of 1- or 2-haloalkyl adamantane with a hydrazine at elevated temperature and pressure, e.g. in a sealed tube at 150°, in accordance with the following
- 10 Reaction Scheme II in which R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are as in formula A and the haloalkyl group is depicted in the 1-position, Hal being halogen:

Reaction Scheme II

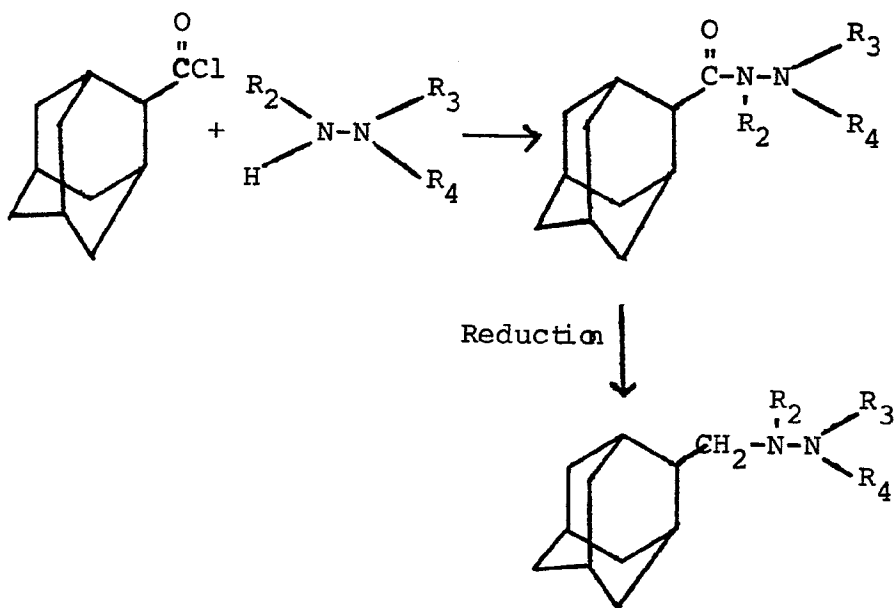


- 15 In this manner (adamant-1-ylmethyl)-hydrazine and 1-(adamant-1'-ylmethyl)-1-methyl-hydrazine were, for example, prepared.

- By yet another embodiment 1- or 2-adamantane carboxylic acid chloride is reacted with a hydrazine
- 20 having at least one free hydrogen and the resulting hydrazide is reduced. This embodiment is shown in the following Reaction Scheme III in which R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are as in formula A and the carboxy chloride group is depicted in the 2-position:

1

Reaction Scheme III



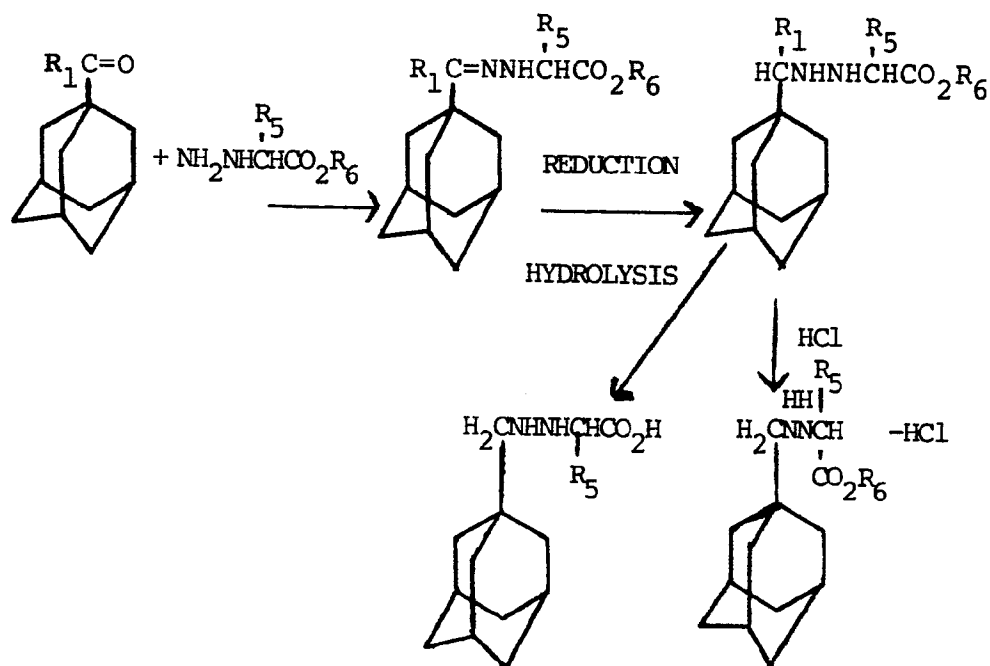
5 For the reduction a hydrogen generating compound such as, for example, lithium aluminium hydride may be used. In this way, using methylhydrazine, 1-(adamant-2'-ylmethyl)-1-methylhydrazine was, for example, prepared.

10 [2-(Adamant-1'-ylmethyl)hydrazino]alkanoic acid esters, their acid addition salts and the corresponding free acids can be prepared in accordance with the invention by a modification of the foregoing embodiment employing a hydrazino acid alkyl ester. This modification is shown in the following Reaction Scheme IV in which  $\text{R}_1$  is as in formula A,  $\text{R}_5$  is hydrogen methyl or ethyl and  $\text{R}_6$  is a lower alkyl and the group  $\text{R}_1\text{C=O}$  is depicted in the 1-position:

15

1

## Reaction Scheme IV



For the reduction a hydrogen generating compound such as, e.g., sodium cyanoborohydride may, for example, be used. The hydrolysis is best effected under mild conditions, e.g. by ion exchange or by refluxing with conc. HCl. A suitable ion-exchanger is, for example, the one known by the commercial designation "Amberlite I R 120 (H)".

As representative examples in this way were synthesized:

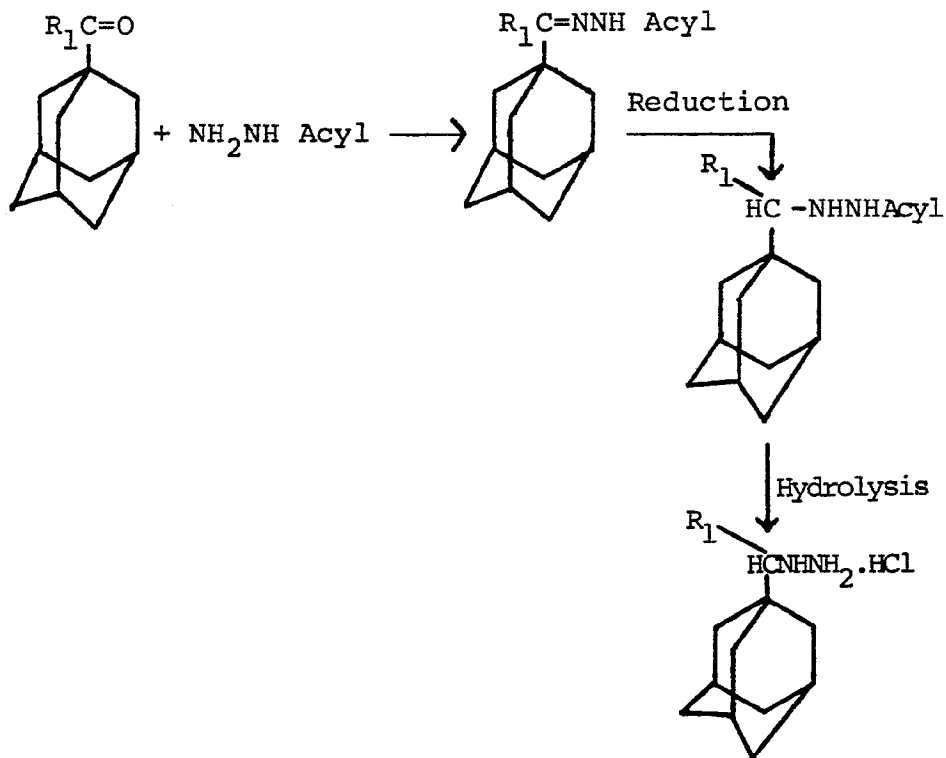
Ethyl [2-(adamant-1'-ylmethyl)hydrazino]acetate  
[2-(adamant-1-ylmethyl)hydrazine]acetic acid, and  
α-[2-(adamant-1'-ylmethyl)hydrazino]butanoic acid.

Attempts at using in the above embodiment free hydrazino acids were unsuccessful, presumably due

1 to their existence as zwitterions which destroys  
the nucleophilic character of the hydrazine.

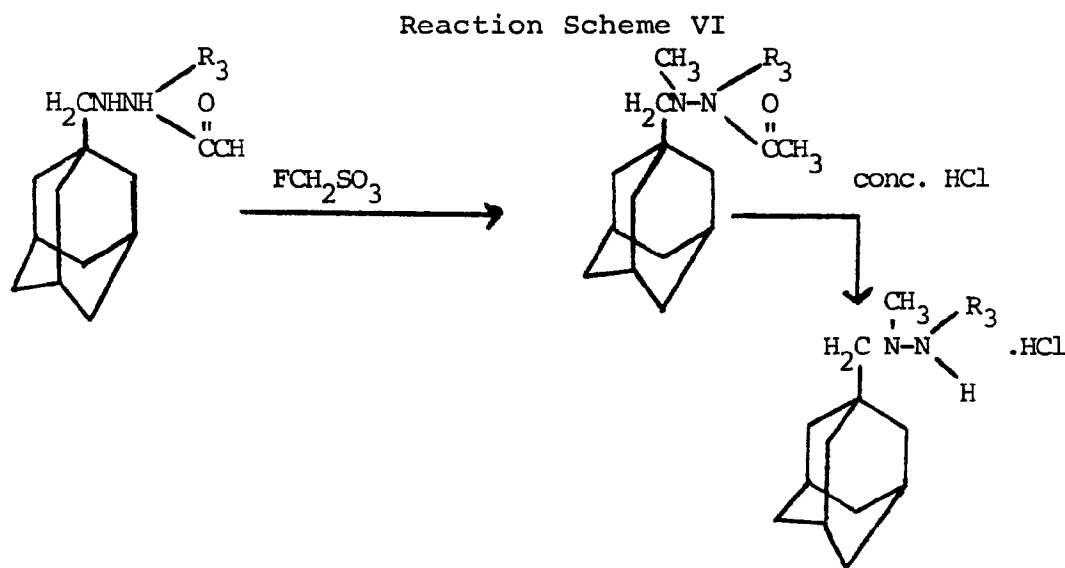
By yet another embodiment for the prepara-  
tion of a compound of formula A in which  $R_1$  and  $R_2$   
5 are hydrogen, a compound of either of formulae B  
and C is reacted with an acyl protected hydrazine in  
which the non-protected nitrogen does not bear any  
substituent, the resulting protected hydrazone is  
reduced and the protected adamantylhydrazine so  
10 obtained is hydrolyzed. This embodiment is shown  
in the following Reaction Scheme V in which the  
 $R_1C=O$  group is depicted in the 1-position:

Reaction Scheme V



1 For the reduction it is again possible to  
 use, for example, a hydrogen generating compound  
 such as, e.g., sodium cyanoborohydride. For the  
 hydrolysis of the acyl group a strong mineral acid  
 5 such as, for example, hydrochloric acid can be used.  
 In this way (adamant-1-ylmethyl)hydrazine was for  
 example, prepared.

By a modification of the above embodiment  
 the acylated hydrazine is N-alkylated prior to  
 10 hydrolysis. For the alkylation it is possible to  
 use, for example, a methyl- or ethylfluorosulfonate.  
 The N-alkylated hydrazine is then hydrolyzed as  
 above. This modification is shown in the following  
 Reaction Scheme VI in which  $R_2$  is as defined in  
 15 formula A and the hydrazino moiety is depicted in  
 the 1-position and the alkylating agent is methyl-  
 fluorosulfonate:



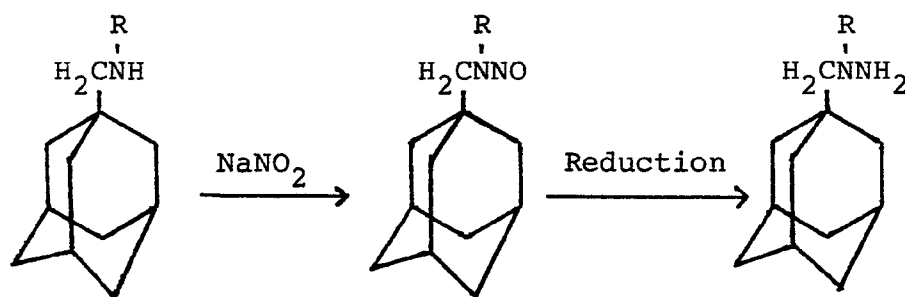
20 In this way 1-(adamant-1'-ylmethyl)-1,2-  
 dimethylhydrazine was, for example, prepared.

By yet another embodiment for the preparation  
 of a compound of either formulae B and C in which  $R_3$

1 and  $R_4$  are both hydrogen but  $R_2$  is not hydrogen, a  
nitrogen-nitrogen bond is formed between a suitable  
disubstituted amine and an aminating agent, e.g.  
sodium nitrite followed by reduction with a reducing  
5 agent, such as lithium aluminium hydride.

For example, (adamant-1'-ylmethyl)isopropyl-  
amine was reacted under acidic conditions with  
sodium nitrite and the resulting N-nitroso compound  
reduced with lithium aluminium hydride to yield  
10 1-(adamant-1'-ylmethyl)-1-isopropylhydrazine.  
(Scheme VII, R = isopropyl for example).

Reaction Scheme VII

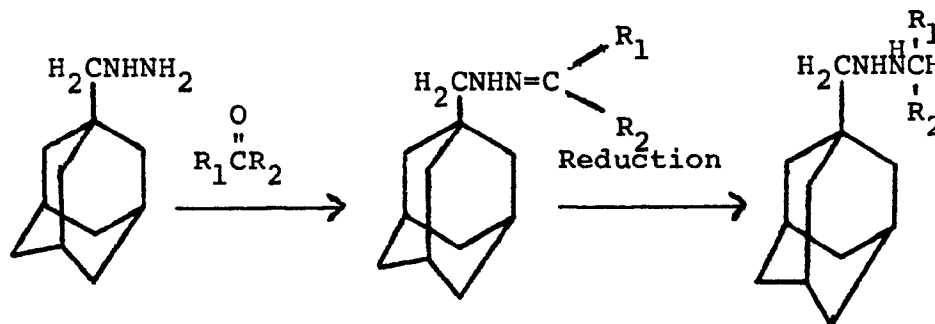


Where in any compound according to the  
15 present invention obtained in accordance with any  
of the foregoing methods a free hydrogen atom of  
the hydrazine moiety is to be substituted, such  
substitution may be effected in accordance with  
known methods, e.g. alkylation with suitable alkyl-  
20 ating agents such as treatment with a powerful base  
followed by an alkyl halide. For example, 1-(adamant-  
1'-ylmethylamino)pyrrolidine obtained, e.g. in accord-  
ance with Scheme I, yields upon treatment with  
butyllithium in dry tetrahydrofuran followed by one  
25 equivalent of methyl iodide the corresponding  
1-[(adamant-1'-ylmethyl)methylamino]pyrrolidine.

1 Furthermore, alkylation of any compound  
according to the present invention containing one  
unsubstituted nitrogen in the hydrazine moiety may  
also be accomplished by condensing said (adamantyl-  
5 methyl)hydrazine with a suitable aldehyde or ketone.  
The resulting hydrazone may be reduced by any of  
the classical reduction methods employed in reaction  
Scheme I. For example (adamantyl-1'-ylmethyl)-  
10 hydrazone obtained, e.g. in accordance with Reaction  
Scheme II, yields upon treatment with acetone, and  
subsequent reduction with sodium cyanoborohydride,  
the corresponding 1-(adamant-1'-ylmethyl)-2-isopropyl-  
hydrazine (see Scheme VIII,  $R_1 = R_2 = \text{CH}_3$  for example  
only).

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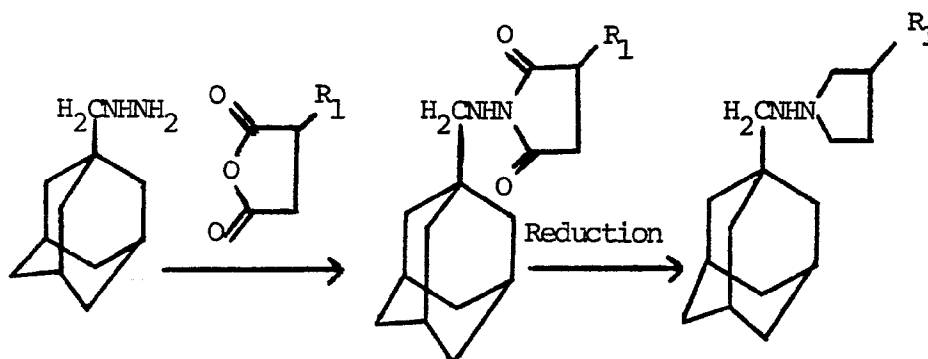
Reaction Scheme VIII



A further modification of the aforementioned alkylation  
uses a cyclic carboxylic acid anhydride for example,  
as an alkylating agent. The resulting cyclic  
20 hydrazide is then reduced in a strong reducing agent  
such as lithium aluminiumhydride. For example,  
(adamant-1'-ylmethyl)hydrazine was treated with methyl-  
succinic anhydride in refluxing toluene with provision  
for water removal. The resulting hydrazide was  
25 reduced with lithium aluminium hydride to yield 1-  
(adamant-1'-ylmethylamino)-3-methylpyrrolidine  
(Scheme IX,  $R_1 = \text{CH}_3$  for example).

1

## Reaction Scheme IX



Quite generally, compounds according to the invention in which the hydrazine moiety is mono-substituted may be converted into di-substituted compounds where the substituent is either on the same nitrogen atom or on different nitrogen atoms and any compound according to the invention in which the hydrazine moiety is di-substituted may be converted by further substitution into the corresponding compound in which the hydrazine moiety is tri-substituted.

In the methods of preparation described hereinbefore the compounds according to the invention are obtained either in the free base form or as acid addition salts. Where a free base is obtained it can be converted into an acid addition salt by reaction with a pharmaceutically acceptable acid as known per se and conversely, where the product first obtained is an acid addition salt and the free base is desired the salt is converted into the free base by reaction with a base, again as known per se.

Furthermore, it is possible to convert an acid addition salt of a compound of formula A into a different one.

1           Novel compounds according to the invention  
of the general formula A possess valuable anti-  
fungal (human and plant), antiviral, anti-  
protosoal and antimicrobial properties. Compounds  
5   according to the invention are also active against  
infections caused by such viruses as vaccinia,  
herpes simplex or influenza or by protozoan  
parasites such as leishmania and trypanosoma, or  
by microorganisms such as leptospira, and also  
10   possess central nervous system (CNS) activity.

For administration to patients the novel  
compounds according to the invention are compounded  
with pharmaceutically acceptable carriers and, if  
desired, with other pharmaceutically active  
15   substances and/or pharmaceutically conventional  
adjuvants.

The invention also provides compositions  
containing each as active ingredient a compound of  
formula A together with an acceptable carrier.  
20   Where such compositions are pharmaceutical the  
carrier must be pharmaceutically acceptable. In  
case of veterinary compositions or compositions for  
agricultural use the carriers are selected  
accordingly.

25           The invention is illustrated by the following  
examples to which it is not limited, all temperature  
indications being in centigrade.

1

Example 11-(Adamant-1'-ylmethyl)-2-methylhydrazine hydrochloride

A methanolic solution of 1.2 g (7 mmol) of 1-adamantylaldehyde and 1 g (21 mmol) of methylhydrazine was refluxed for 2 hours at which time the volatiles were removed in vacuo. The resulting oil was taken up in ether, washed with water, dried and concentrated to 1.4 g hydrazone which was reduced with an excess of sodium cyanoborohydride in slightly acidified ethanol. After 1 hour the reaction was basified with 10% aq. sodium hydroxide. Solvent evaporation followed by ether extraction, water wash and treatment with hydrogen chloride gave 900 mg (56%) of the title compound.

mp 236 - 238<sup>o</sup> (d), (ethylacetate/isopropanol)  
nmr (CDCl<sub>3</sub>/TFA)  $\delta$  2.9 (s, 3H), 2.8 (s, 2H).  
Anal calcd for C<sub>12</sub>H<sub>23</sub>N<sub>2</sub>Cl:  
C, 62.49; H, 10.06; N, 12.16; Cl, 15.38;  
Found: C, 62.62; H, 10.03; N, 12.55; Cl, 15.65.

Compounds described in the following Examples 2 to 13 and 24 to 36 were prepared by the same method as Example 1, except that 1 equivalent of the appropriate hydrazine derivative was used.

Example 2

25 1-(Adamant-1'-ylmethyl)-2,2-dimethylhydrazine hydrochloride hemi-hydrate

The title compound was obtained in 35% yield by using 1,1-dimethylhydrazine instead of methylhydrazine as in Example 1.

30 mp 284 - 5<sup>o</sup> (d), (isopropanol)  
nmr (CDCl<sub>3</sub>/TFA)  $\delta$  3.0 (s., 6H), 2.7 (s, 2H).

1           Anal calcd for  $C_{13}H_{26}N_2O_{1/2}Cl$ :  
               C, 61.54; H, 10.25; N, 11.09; Cl, 14.00;  
               Found: C, 61.21; H, 10.65; N, 11.49; Cl, 13.76.

Example 3

5       1-(Adamant-1'-ylmethyl)-2-benzylhydrazine hydrochloride

          The title compound was obtained in 54% yield  
 by using benzylhydrazine instead of methylhydrazine  
 as in Example 1.

          mp 232-5° (d), (isopropanol/water)  
 10       nmr ( $CDCl_3$ /TFA)  $\delta$  7.3 (s, 5H), 4.3 (s, 2H),  
           2.8 (s, 2H).

          Anal calcd for  $C_{18}H_{27}N_2Cl$ :  
               C, 70.43; H, 8.87; N, 9.13; Cl, 11.57  
               Found: C, 70.26; H, 8.98; N, 9.06; Cl, 11.68

15                               Example 4

1-(Adamant-1'-ylmethyl)-2,2-diphenylhydrazine hydro -  
 chloride

          The title compound was obtained in 48% yield  
 by using 1,1-diphenylhydrazine instead of methyl-  
 20       hydrazine as in Example 1.

          mp 162 - 164° (d), (ethylacetate)  
           nmr ( $CDCl_3$ )  $\delta$  6.9 - 7.6 (m, 10H), 3.0 (s, 2H)  
           mass spectrum ( $m/e$ )  $M^+$  = 332.

Example 5

25       1-(Adamant-1'-ylmethyl)-2-(m-trifluoromethylphenyl)-  
 hydrazine hydrochloride hemi-hydrate

          The title compound was obtained in 52% yield  
 by using (m-trifluoromethylphenyl)hydrazine instead  
 of methylhydrazine as in Example 1.

30       mp 200 - 203° (d), (ethylacetate)  
           nmr ( $CDCl_3$ /TFA)  $\delta$  7.1 - 7.4 (m, 4H);  
           3.0 (s, 2H).

1           Anal calcd for  $C_{18}H_{25}N_2F_3ClO_{1/2}$  :  
              C, 58.42; H, 6.81; N, 7.88; Cl, 9.60  
              Found: C, 58.38; H, 6.78; N, 7.88; Cl, 9.72.

Example 6

5       1-(Adamant-1'-ylmethyl)-2-(o-carboxyphenyl)hydrazine  
          The title compound was obtained in 50% yield  
          by using N-aminoanthranilic acid instead of methyl-  
          hydrazine as in Example 1.

          mp 212 - 3° (d), (ethyl acetate/petroleum  
10           ether).

          nmr ( $CDCl_3$ /TFA)  $\delta$  3.1 (s, 2H).

          Anal calcd for  $C_{18}H_{24}N_2O_2$  :

              C, 71.95; H, 8.06; N, 9.32

          Found: C, 72.00; H, 8.31; N, 9.14.

15           Example 7

1-(Adamant-1'-ylmethylamino)pyrrolidine hydrochloride

          The title compound was obtained in 64% yield  
          by using 1-aminopyrrolidine instead of methyl-  
          hydrazine as in Example 1.

20           mp 260 - 264° (d), (isopropanol)

          nmr ( $CDCl_3$ /TFA)  $\delta$  2.7 (s, 2H).

          Anal calcd for  $C_{15}H_{27}N_2Cl$  :

              C, 66.49; H, 10.04; N, 10.34; Cl, 13.11

          Found: C, 66.62; H, 9.93; N, 10.32; Cl, 13.19.

25           Example 8

1-(Adamant-1'-ylmethylamino)piperidine hydrochloride

          The title compound was obtained in 47% yield  
          by using 1-aminopiperidine instead of methylhydrazine  
          as in Example 1.

1 mp 289 - 291<sup>o</sup> (d), (isopropanol)  
 nmr (CDCl<sub>3</sub>/TFA) δ 2.7 (s, 2H)  
 Anal calcd for C<sub>16</sub>H<sub>29</sub>N<sub>2</sub>Cl:  
           C,67.43; H,10.18; N,9.83; Cl,12.47  
 5 Found: C,67.69; H,10.50; N,9.64; Cl,12.36.

Example 9

4-(Adamant-1'-ylmethylamino)morpholine hydrochloride  
 hemi-hydrate

The title compound was obtained in 45% yield  
 10 by using 4-aminomorpholine instead of methylhydrazine  
 as in Example 1.

mp 274-276<sup>o</sup> (d), (isopropanol)  
 nmr (CDCl<sub>3</sub>/TFA) δ 2.8 (s, 2H).  
 Anal calcd for C<sub>15</sub>H<sub>28</sub>N<sub>2</sub>ClO<sub>1.5</sub>:  
 15           C,60.87; H,9.54; N,9.46; Cl,12.00  
 Found: C,61.10; H,9.37; N,9.80; Cl,11.90.

Example 10

1-(Adamant-1'-ylmethylamino)-4-methylpiperazine  
 dihydrochloride hydrate

20 The title compound was obtained in 35% yield  
 by using 1-amino-4-methylpiperazine instead of  
 methylhydrazine as in Example 1.

mp 286 - 287<sup>o</sup> (d), (ethanol)  
 nmr (CDCl<sub>3</sub>/TFA) δ 2.6 - 4/0 (m, 13H)  
 25 Anal calcd for C<sub>16</sub>H<sub>33</sub>N<sub>3</sub>Cl<sub>2</sub>O:  
           C,54.19; H,9.40; N,11.85; Cl,20.04  
 Found: C,54.52; H,9.12; N,11.18; Cl,20.56.

Example 11

30 1-(Adamant-1'-ylmethylamino)-4-(m-trifluoromethyl-  
 phenyl)piperazine hydrochloride hemi-hydrate

The title compound was obtained in 57% yield  
 by using 1-amino-4-(m-trifluoromethylphenyl)piperazine

1 instead of methylhydrazine as in Example 1.

mp 261 - 265<sup>o</sup> (d), (methanol)

nmr (CDCl<sub>3</sub>/TFA) δ 3.9 (S, 8H), 3.0 (S, 2H)

Anal calcd for C<sub>22</sub>H<sub>32</sub>N<sub>3</sub>ClF<sub>3</sub>O<sub>1/2</sub> :

5 C, 60.21; H, 7.30; N, 9.58; Cl, 8.10; F, 13.00

Found: C, 60.44; H, 7.30; N, 9.62; Cl, 8.22; F, 12.52.

Example 12

1-(Adamant-2'-ylmethyl)-2,2-dimethylhydrazine  
hydrochloride

10 The title compound was obtained in 30% yield  
by using 2-adamantylaldehyde and 1,1-dimethylhydrazine  
instead of 1-adamantylaldehyde and methylhydrazine  
respectively as in Example 1.

mp 217-220<sup>o</sup> (d), (ethyl acetate/methylene  
15 chloride)

nmr (CDCl<sub>3</sub>) δ 3.15 (d, 2H); 2.86 (S, 6H)

Anal calcd for C<sub>13</sub>H<sub>25</sub>N<sub>2</sub>Cl:

N, 11.45; Cl, 14.52

Found: N, 11.43; Cl, 14.46.

20 Example 13

1-(Adamant-2'-ylmethyl)-2-(pyrid-2"-yl)hydrazine  
hydrochloride

The title compound was obtained in 55% yield  
by using 2-adamantylaldehyde and (pyrid-2'-yl)-  
25 hydrazine instead of 1-adamantylaldehyde and methyl-  
hydrazine respectively as in Example 1.

mp 135 - 140<sup>o</sup> (d), (ethyl acetate)

nmr (CDCl<sub>3</sub>/TFA) δ 3.33 - 3.60 (d, 2H).

mass spectrum (m/e) M<sup>+</sup> = 257.

30 Example 14

(Adamant-1-ylmethyl)hydrazine hydrochloride

4.0 g (120 mmol) of anhydrous hydrazine and  
2.3 g (12 mmol) of 1-chloromethyladamantane were  
introduced into a sealable tube under nitrogen  
atmosphere. The tube was sealed and heated at  
5 150° for 16 hours. After cooling to room temperature  
the contents were suspended in methanol, treated  
with a solution 0.5 g of sodium hydroxide in 1.5 ml  
of water, and the volatiles removed in vacuo. The  
resulting solid was extracted with ether and the  
10 solution dried with magnesium sulfate and treated  
with hydrogen chloride to give 1 g of the title  
compound (38% yield).

mp 256 - 258° (d), (isopropanol)  
nmr (CDCl<sub>3</sub>/TFA) δ 3.3 (s, 2H)  
15 Anal calcd for C<sub>11</sub>H<sub>21</sub>N<sub>2</sub>Cl:  
C, 60.97; H, 9.78; N, 12.94; Cl, 16.37  
Found: C, 61.20; H, 9.71; N, 12.85; Cl, 16.77.

#### Example 15

20 1-Methyl-1-(adamant-1'-ylmethyl)hydrazine hydrochloride  
hydrate

The procedure of Example 14 was followed using  
methylhydrazine instead of anhydrous hydrazine. The  
resulting ether solution containing the 2 possible  
condensation products, the title compound and the  
25 2-methyl isomer, was stored at about 5° for 4 days. There-  
after treatment with hydrogen chloride caused the  
title compound to crystallize from the solution in  
95% purity (35% yield).

mp 196-197° (d), (ethyl acetate/methylene  
30 chloride)  
nmr (CDCl<sub>3</sub>/TFA) δ 3.05 (s, 3H), 2.95 (s, 2H)

1           Anal calcd for  $C_{12}H_{25}N_2ClO$ :  
               C, 57.90; H, 10.13; N, 11.25; Cl, 14.27  
               Found: C, 57.86; H, 10.24; N, 11.09; Cl, 14.12.

Example 16

5   1-Methyl-1-(adamant-2'-ylmethyl)hydrazine  
      hydrochloride

          To 7 g of methylhydrazine in 25 ml of ethyl-  
           acetate was added 5.4 g of 2-adamantylcarboxylic acid  
           chloride in 25 ml of the same solvent. After 15  
 10   minutes additional stirring the reaction was washed  
       with a solution of ammonium chloride and concentrated  
       to 4.5 g of hydrazide. The hydrazide was reduced  
       with 1.1 g of lithium aluminum hydride in refluxing  
       tetrahydrofuran for 1/2 hour.

15           After cooling the reaction was poured into  
           aqueous ammonium chloride and extracted 2 times with  
           methylenechloride. The combined organic layers were  
           dried over magnesium sulfate and solvent removed in  
           vacuo. The resulting oil was dissolved in ether and  
 20   treated with hydrogen chloride to give 2.4 g of the title  
       compound (40% yield).

          mp 224-6° (d), (ethyl acetate)  
           nmr ( $CDCl_3$ )  $\delta$  3.28 (d, 2H), 2.96 (s, 3H)  
           Anal calcd for  $C_{12}H_{23}ClN_2$ :

25           C, 62.47; H, 9.97; N, 12.14; Cl, 15.40  
           Found: C, 62.67; H, 9.95; N, 12.10; Cl, 15.10.

Example 17

Ethyl [(2-adamant-1'-ylmethyl)hydrazino]acetate  
      hydrochloride

30           The procedure of Example 1 was followed using  
           ethyl hydrazino-acetate instead of methylhydrazine,  
           to give the title compound in 24% yield.

1 mp 188-190<sup>o</sup> (d), (ethyl acetate)  
 nmr (CDCl<sub>3</sub>) δ 4.2 (q, 2H); 4.0 (s, 1H);  
 2.9 (s, 1H); 1.3 (t, 3H)  
 Anal calcd for C<sub>15</sub>H<sub>27</sub>N<sub>2</sub>O<sub>2</sub>Cl:  
 5 C, 59.50; H, 8.92  
 Found: C, 59.36; H, 8.70.

Example 18

[2-(Adamantyl-1'-ylmethyl)hydrazino]acetic acid  
 hydrochloride

10 The hydrazino ester hydrochloride (3 g) of  
 Example 17 was hydrolyzed with 2 g of Amberlite IR  
 120 (H) in refluxing water for 5 hrs to give the  
 title compound in 25% yield after filtration and  
 evaporation of solvent.

15 mp 178-179<sup>o</sup> (isopropanol, ethyl acetate)  
 nmr (CDCl<sub>3</sub>/TFA) δ 4.0 (s, 2H), 3.0 (s, 2H).  
 Anal calcd for C<sub>13</sub>H<sub>23</sub>N<sub>2</sub>O<sub>2</sub>Cl:  
 C, 56.79; H, 8.45; N, 10.19  
 Found: C, 57.00; H, 8.19; N, 9.78.

Example 19

(Adamant-1-ylmethyl)hydrazine hydrochloride

The title compound was also prepared in analogy  
 with Example 1 using acetylhydrazine instead of  
 methylhydrazine. The acetyl group was cleaved by 2  
 25 hours reflux in conc. HCl, giving a product with  
 identical properties to those of Example 14  
 (58% yield).

Example 20

1,2-Dimethyl-1-(adamant-1'-ylmethyl)hydrazine  
 hydrochloride

30 The procedure of Example 1 was followed using  
 1-acetyl-1-methylhydrazine instead of methylhydrazine.  
 After reduction, the resulting acetylhydrazine was  
 treated with one equivalent of methyl fluorosulfonate

1 in methyl acetate at 0°. After stirring for 2 hours  
the reaction was poured into 10% aq sodium hydroxide  
and extracted with methylene chloride, the solvent  
removed and the residue was treated with conc. HCl  
5 and refluxed for 1 hour to give the title compound  
upon cooling.

mp 176-179° (d), (ethyl acetate)

nmr (CDCl<sub>3</sub>) δ 2.8 (s, 3H); 2.7 (s, 3H);

2.6 (s, 2H)

10 Anal calcd for C<sub>13</sub>H<sub>25</sub>N<sub>2</sub>Cl:

C, 63.75; H, 10.30; N, 11.44; Cl, 14.51

Found: C, 63.81; H, 10.40; N, 11.44; Cl, 14.94.

#### Example 21

##### [1-(Adamant-1'-yl)ethyl]hydrazine hydrochloride

15 The procedure of Example 19 was followed using  
acetyladamantane instead of 1-adamantylaldehyde to  
give the title compound in 26% yield.

mp 212-214° (d), (isopropanol)

nmr (CDCl<sub>3</sub>/TFA) δ 2.95 (q, 1H, J = 7Hz),

20 (d, 3H, J = 7Hz).

Anal calcd for C<sub>12</sub>H<sub>23</sub>N<sub>2</sub>Cl:

C, 62.49; H, 10.06; N, 12.16; Cl, 15.38

Found: C, 62.23; H, 10.03; N, 12.61; Cl, 15.09.

#### 25 Example 22

##### 1-[1'-(Adamant-1"-yl)ethyl]-2-methylhydrazine hydrochloride

A solution of 1.8 g (10 mmol) of acetyl-  
adamantane and 600 mg (13 mmol) of methylhydrazine was  
30 refluxed in 150 ml of benzene with continuous removal  
of water via a Dean-Stark Apparatus.

After 2 1/2 hours the reaction was cooled the  
volatiles removed in vacuo leaving 1.7 g oil which was  
reduced with 800 mg of sodium cyanoborohydride according

1 to the procedure of Example 1. Treatment of the  
resulting ether solution with hydrogen chloride gave  
900 mg of the title compound (37% yield).

mp 239 - 241<sup>o</sup> (d), (acetone)

5 nmr (CDCl<sub>3</sub>/TFA) δ 1.3 (d, 3H)

Anal calcd for C<sub>13</sub>H<sub>25</sub>N<sub>2</sub>Cl:

C, 63.75; H, 10.30; N, 11.44; Cl, 14.49

Found: C, 63.71; H, 10.60; N, 11.29; Cl, 14.90.

#### Example 23

10 1-[1'-(Adamant-1"-yl)ethyl]-2-(m-trifluoromethylphenyl)-  
hydrazine hydrochloride hemi-hydrate

Following the procedure of Example 5, but using  
1-acetyladamantane instead of 1-adamantylaldehyde the  
title compound was obtained in 37% yield.

15 mp 198 - 200<sup>o</sup> (d), (ethyl acetate)

nmr (DMSO-d<sub>6</sub>) δ 1.25 (d, 3H)

Anal calcd for C<sub>19</sub>H<sub>27</sub>N<sub>2</sub>ClF<sub>3</sub>O<sub>1</sub><sup>1</sup>/<sub>2</sub>:

C, 59.42; H, 7.08; N, 7.29

Found: C, 59.27; H, 6.92; N, 7.06.

#### 20 Example 24

1-(Adamant-1'-ylmethyl)-2-[1"-(2"-hydroxyethyl)]hydrazine  
hydrochloride

The title compound was obtained in 42% yield  
by using 2-hydrazinoethanol instead of methylhydrazine  
25 as in Example 1 except that the resulting hydrazone  
was reduced with 50 psi H<sub>2</sub> on 10% palladium on carbon.

mp 194<sup>o</sup> (d), (methanol/ethylacetate)

nmr (CDCl<sub>3</sub>/TFA) δ 3.4-4.4 (m, 2H), 3.3-3.6

(m, 2H); 3.0 (s, 2H)

30 Anal calcd for C<sub>13</sub>H<sub>25</sub>ClN<sub>2</sub>O:

C, 59.88; H, 9.60; N, 10.75; Cl, 13.63

Found: C, 59.71; H, 9.74; N, 10.94; Cl, 13.65.

1

Example 251-(Adamant-1'-ylmethyl)-2-phenethylhydrazine  
dihydrate

5 The title compound was obtained in 29% yield  
by using phenethylhydrazine instead of methyl-  
hydrazine as in Example 1.

mp 231-235° (d), (isopropanol/ether)

nmr (CDCl<sub>3</sub>/TFA) δ 7.2 (s, 5H); 3.4 (d, 2H);  
2.7 (s, 2H)

10

Anal calcd for C<sub>19</sub>H<sub>32</sub>N<sub>2</sub>O<sub>2</sub>:

C, 71.21; H, 10.05; N, 8.74

Found: C, 71.62; H, 10.37; N, 8.27.

Example 26

15 1-(Adamant-1'-ylmethyl)-2-(p-bromophenyl)hydrazine  
hydrochloride

The title compound was obtained in 75% yield  
by using p-bromophenylhydrazine instead of methyl-  
hydrazine as in Example 1.

mp 214-215° (d), (isopropanol/methanol)

20

nmr (CDCl<sub>3</sub>/TFA) δ 7.18 (q, 4H); 2.95 (s, 2H)

Anal calcd for C<sub>17</sub>H<sub>24</sub>N<sub>2</sub>BrCl:

C, 54.92; H, 6.44; N, 7.52; Cl, 9.50; Br, 21.51

Found: C, 54.53; H, 6.37; N, 7.31; Cl, 9.25; Br, 22.02

Example 27

25 1-(Adamant-1'-ylmethyl)-2-[4"-(7"-chloroquinolinyl)]-  
hydrazine hemi-hydrate

The title compound was obtained in 17% yield  
by using 7-chloro-4-hydrazinoquinoline instead of  
methylhydrazine as in Example 1.

30

mp 308-312° (d), (isopropanol)

nmr (CDCl<sub>3</sub>) δ 8.6-8.9 (m, 1H), 7.9-8.2 (m, 2H),  
7.0-7.4 (m, 2H), 2.7 (br.s., 2H)

1                   Anal calcd for  $C_{20}H_{26}N_3Cl_2O_{\frac{1}{2}}$  :  
                                   C, 61.98; H, 6.73; N, 10.84  
                                   Found: C, 61.52; H, 6.17; N, 10.39.

Example 28

5    1-(Adamant-1'-ylmethylamino)-2-methylpyrrolidine  
       hydrochloride

          The title compound was obtained in 58% yield  
           by using 1-amino-2-methylpyrrolidine instead of  
           methylhydrazine as in Example 1.

10           mp 254-256° (d), (isopropanol/ether)  
               nmr (CDCl<sub>3</sub>/TFA) δ 3.2-4.0 (m, 3H); 2.6 (s, 2H);  
                   1.4-2.5 (m, 22H)  
               mass spectrum (m/e) M+ = 248 (64), 233 (78),  
                   135 (65), 133 (100), 107 (38).

Example 29

15    1-(Adamant-1'-ylmethylamino)homopiperidine  
       hydrochloride quarterhydrate

          The title compound was synthesized in 43% yield  
           by using 1-amino-homopiperidine instead of methyl-  
           hydrazine as in Example 1.

20           mp 265° (d), (isopropanol)  
               nmr (CDCl<sub>3</sub>) δ 2.75 (m, 4H), 2.5 (s, 2H)  
               Anal calcd for  $C_{17}H_{31}N_2Cl \cdot \frac{1}{4} H_2O$ :  
                   C, 67.20; H, 10.20; N, 9.22  
               Found: C, 67.24; H, 10.19; N, 9.07.

Example 30

30    1-(Adamant-1'-ylmethylamino)heptamethyleneimine  
       hydrochloride

          The title compound was obtained in 16% yield  
           using 1-aminoheptamethyleneimine instead of methyl-  
           hydrazine as in Example 1, except that the resulting  
           hydrazone was reduced with lithium aluminium hydride.

1 mp 285-261<sup>o</sup> (d), (isopropanol/ethyl  
acetate)  
nmr (CDCl<sub>3</sub>) δ 3.0-3.6 (m, 4H),  
2.7 (br.s. 2H)  
5 Anal calcd for C<sub>18</sub>H<sub>33</sub>N<sub>2</sub>Cl:  
N, 8.96  
Found: N, 8.81.

Example 31

1-(Adamant-2'-ylmethylamino)pyrrolidine hydrochloride

10 The title compound was obtained in 35%  
yield by using 2-adamantylaldehyde and 1-amino-  
pyrrolidine instead of 1-adamantylaldehyde and methyl-  
hydrazine respectively as in Example 1 except that  
the resulting hydrazone was reduced with lithium  
15 aluminium hydride.

mp 235<sup>o</sup> (d), (ethylacetate)  
nmr (CDCl<sub>3</sub>) δ 2.8-4.0 (m, 6H)  
Anal calcd for C<sub>15</sub>H<sub>27</sub>N<sub>2</sub>Cl:  
C, 66.54; H, 9.98; N, 10.35; Cl, 13.12  
20 Found: C, 66.41; H, 9.74; N, 10.04; Cl, 13.12.

Example 32

1-(Adamant-2'-ylmethylamino)piperidine hydrochloride

The title compound was obtained in 20%  
yield using 2-adamantylaldehyde and 1-aminopiperidine  
25 instead of 1-adamantylaldehyde and methylhydrazine as  
in Example 1 except that the resulting hydrazone was  
reduced with lithium aluminium hydride.

mp 263-264<sup>o</sup> (d), (isopropanol)  
nmr (CDCl<sub>3</sub>) δ 3.1-3.5 (m, 6H)  
30 Anal calcd for C<sub>16</sub>H<sub>29</sub>N<sub>2</sub>Cl:  
C, 67.48; H, 10.19; N, 9.84; Cl, 12.47  
Found: C, 67.31; H, 10.35; N, 9.78; Cl, 12.91.

1

Example 331-(Adamant-2'-ylmethyl)-2-(1"-adamantyl)hydrazine hydrochloride hemihydrate

5 The title compound was obtained in 5% yield using 2-adamantylaldehyde and 1-adamantylhydrazine instead of 1-adamantylaldehyde and methylhydrazine as in Example 1, except that the resulting hydrazone was reduced with lithium aluminum hydride.

mp 290-292<sup>o</sup> (d), (methanol)  
10 nmr (CDCl<sub>3</sub>) δ 3.1 (d, 2H); 1.5-2.5 (m, 30H)

Anal calcd for C<sub>21</sub>H<sub>36</sub>N<sub>2</sub>ClO<sub>1/2</sub>:

C, 70.09; H, 10.01; N, 7.78;

Found: C, 70.26; H, 10.10; N, 8.11

Example 34

15 1-(Adamant-1'-ylmethylamino)thiomorpholine hydrochloride

The title compound was obtained in 38% yield using 1-aminothiomorpholine instead of methylhydrazine as in Example 1.

mp 269-272<sup>o</sup> (d), (isopropanol/ethylacetate)  
20 nmr (CDCl<sub>3</sub>/TFA) δ 3.4-3.6 (m, 4H), 2.8-3.1 (m, 4H), 2.7 (br.s. 2H)

Anal calcd for C<sub>15</sub>H<sub>27</sub>N<sub>2</sub>SCl :

C, 59.50; H, 8.92; N, 9.25; Cl, 11.72; S, 10.57

Found: C, 59.23; H, 8.73; N, 8.91; Cl, 12.00; S, 11.04

25

Example 351-(Adamant-1'-ylmethylamino)hydantoin

The title compound was obtained in 10% yield using 1-aminohydantoin sulfate instead of methylhydrazine as in Example 1.

30 mp 193-194<sup>o</sup> (d), (isopropanol)

nmr (CDCl<sub>3</sub>/TFA) δ 4.5 (s, 2H); 3.2 (s, 2H).

1           Anal calcd for  $C_{14}H_{22}N_3O_2$ :  
               C, 63.59; H, 8.40; N, 15.89  
               Found: C, 63.06; H, 8.18; N, 15.67.

Example 36

5    1-(Adamant-1'-ylmethyl)-2-butylhydrazine  
       hydrochloride hemi-demi-hydrate

          The title compound was obtained in 39% yield  
           using n-butylhydrazine hydrochloride (prepared in situ  
           from the oxalate and conc. HCl) instead of methyl-  
 10   hydrazine as in Example 1.

          mp 236-240° (d), (isopropanol)  
           nmr ( $CDCl_3$ /TFA)  $\delta$  3.2 (t, 2H); 2.7 (s, 2H)  
           Anal calcd for  $C_{15}H_{29.5}N_2ClO_{1/4}$ :

          C, 64.98; H, 10.64; N, 10.10  
 15       Found: C, 64.71; H, 10.38; N, 10.04.

Example 37

$\alpha$ -[2-(Adamant-1'-ylmethyl)hydrazino]butanoic acid  
hydrochloride

          A methanolic solution of 1.64 g (10 mmol) of  
 20   1-adamantylaldehyde, 1.8 g (10 mmol) of ethyl  
       hydrazinobutanoate hydrochloride and 5.6 g (10 mmol)  
       of KOH was refluxed for 2 1/2 hrs. The volatiles  
       were removed in vacuo and the residue partitioned  
       between methylene chloride and water. The organic  
 25   layer was dried and concentrated to 3 g of  
       hydrazone which was reduced with 750 mg of sodium  
       cyanoborohydride. The resulting hydrazino ester was  
       hydrolyzed by refluxing in 5 ml of conc. HCl for  
       30 min. Evaporation of the volatiles give the title  
 30   compound in 75% yield.

          mp 188-190° (d), (isopropanol/ethyl acetate)  
           nmr ( $CDCl_3$ /TFA)  $\delta$  4.0 (t, 1H); 2.9 (s, 2H);  
               1.0 (t, 3H).

1           Anal calcd for  $C_{15}H_{27}N_2O_2Cl$ :  
               C, 59.46; H, 8.99; N, 9.25; Cl, 11.73  
               Found: C, 59.52; H, 8.81; N, 9.20; Cl, 12.85.

Example 38

5    1-(Adamant-1'-ylmethyl)-1-isopropylhydrazine  
       hydrochloride

          A methanolic solution of 3 g (18 mmol) of  
 adamant-1-ylmethylamine and 2 g (34 mmol) of acetone  
 was refluxed for 2 1/2 hours and the volatiles  
 10 removed to give 3.6 g of imine, which was reduced  
 with 550 mg of sodium borohydride in refluxing  
 ethanol. After 1 hr. the volatiles were removed in  
 vacuo and the residue partitioned between ether and  
 water. The organic layer was dried and concentrated  
 15 to 3.3 g of (adamant-1-ylmethyl)isopropylamine which  
 was suspended in 30 ml of  $H_2O$  at  $0^\circ$  and 50% aq  $H_2SO_4$   
 added until the suspension was acidic. At this time  
 a solution of 1.5 g of sodium nitrite in 10 ml of  
 $H_2O$  was added forming a white precipitate. After  
 20 1 hr. at room temperature the mixture was extracted  
 twice with methylene chloride and the organic  
 layers dried and concentrated to 4.0 g of nitroso-  
 amine which was subsequently reduced with 900 mg  
 lithium aluminium hydride in refluxing tetra-  
 25 hydrofuran for 2 hrs. After cooling, sodium-  
 sulfate decahydrate was added until bubbling ceased.  
 Filtration and evaporation of the filtrate yielded  
 2.7 g of oil which was dissolved in ether and treated  
 with HCl. The title compound was obtained in 58%  
 30 yield by filtration.

mp  $263-264^\circ$  (d), (isopropanol)  
 nmr ( $CDCl_3$ /TFA)  $\delta$  3.5 (m, 1H); 2.8 (s, 2H);  
 1.3 (d, 6H)

1           Anal calcd for  $C_{14}H_{27}N_2Cl$ :  
                   C, 64.96; H, 10.51; N, 10.82; Cl, 13.72  
           Found: C, 64.70; H, 10.64; N, 10.71; Cl, 13.50.

Example 39

5    1-[(Adamant-1'-ylmethyl)methylaminolpyrrolidine  
       hydrochloride

          To a solution of 1.7 g (7.3 mmol) of 1-  
       (adamant-1'-ylmethylamino)pyrrolidine in dry tetra-  
       hydrofuran under  $N_2$  at  $0^\circ$  was added 6 ml (7.3 mmol)  
 10   of 1.6 M butyllithium, followed in 5 min. by 0.8 ml  
       (12.4 mmol) of methyl iodide. After 15 min. at room  
       temperature water was added and the mixture  
       concentrated in vacuo and twice extracted with  
       ether. The dried ether layers were combined  
 15   treated with HCl to give the title compound which was  
       obtained in 45% yield by filtration.

          mp 227-228 $^\circ$  (d), (isopropanol/ethyl acetate)  
           nmr ( $CDCl_3$ )  $\delta$  3.4 (m, 4H); 2.8 (s, 3H);  
                   2.5 (s, 2H)

20    Anal calcd for  $C_{16}H_{29}N_2Cl$ :  
                   C, 67.44; H, 10.26; N, 9.83; Cl, 12.47  
       Found: C, 67.18; H, 9.97; N, 9.99; Cl, 12.36.

Example 40

25   1-(Adamant-1'-ylmethyl)-2-isopropylhydrazine  
       hydrochloride

          A methanolic solution of 1.4 g (6.5 mmol) of  
       adamant-1-ylmethylhydrazine hydrochloride and 1 g  
       (17 mmol) of acetone was refluxed for 4 hrs. The  
       resulting hydrazone was reduced with sodium cyano-  
 30   borohydride in ethanol. After 1 hr the reaction was  
       basified with 10% NaOH, concentrated, and the  
       residue partitioned between water and methylene  
       chloride. The dried organic phase was concentrated

1 dissolved in ether and treated with HCl. The title  
compound was obtained in 25% yield by filtration.

mp 237-242<sup>o</sup> (ethylacetate/methanol)

nmr (CDCl<sub>3</sub>/TFA) δ 3.5 (m, 1H); 2.6 (s, 2H);

5 1.4 (d, 6H)

Anal calcd for C<sub>14</sub>H<sub>27</sub>N<sub>2</sub>Cl:

C,64.99; H,10.44; N,10.83; Cl,13.75

Found: C,64.94; H,10.17; N,10.91; Cl,13.30.

#### Example 41

10 1-(Adamant-1'-ylmethylamino)-3-methylpyrrolidine  
hydrochloride hemi-hydrate

A solution of 1.1 g (6.1 mmol) of adamant-1-ylmethylhydrazine and 700 mg (6.1 mmol) of methylsuccinic anhydride was refluxed in toluene with  
15 continuous removal of water via a Dean-Stark  
apparatus. After 2 1/2 hrs the solution was diluted  
with ether, washed with saturated sodium carbonate,  
dried and concentrated to 1.1 g succinimide, which  
was reduced with 400 mg of lithium aluminium hydride  
20 in refluxing tetrahydrofuran for 3 hrs at which  
time the suspension was cooled and sodium sulfate  
decahydrate added until bubbling ceased. The  
mixture was then filtered and the filtrate concentra-  
ted and dissolved in ether and treated with HCl. The  
25 title compound was obtained in 22% yield by filtration.

mp 210-215<sup>o</sup> (d), (ethylacetate)

nmr (CDCl<sub>3</sub>) δ 8.2 (m, 3H, exch); 3.0-3.9 (m, 4H);

2.9 (s, 2H); 1.2 (d, 3H)

Anal calcd for C<sub>16</sub>H<sub>30</sub>N<sub>2</sub>ClO<sub>1/2</sub>:

30 C,65.37; H,10.28; N,9.53

Found: C,65.39; H,10.28; N,9.91.

1           In the following test results are given  
which demonstrate the antimicrobial, antiprotozoan,  
CNS, antifungal and antiviral activities of  
compounds according to the invention.

5           Antimicrobial activity was demonstrated on  
mycoplasma; antiprotozoan activity on Leishmania  
and Trypanosoma; CNS activity on albino rats and  
albino mice; antifungal activity on human fungi and  
yeast; and antiviral activity on HSV-1 (Herpes  
10 Simplex) and on influenza virus.

          The following are the results:

1

ANTIMYCOPLASMA ACTIVITY

Some of the compounds were tested against 4 mycoplasma. The method used was as follows:

5

Microorganisms: 1. M. gallisepticum  
2. M. capricolum  
3. M. hominis  
4. A. laidlawii

Assay:

50% inhibition of growth in liquid medium.

10

Results:

The tested compounds of Examples Nos. 3, 7, 8, 38, 25, were found to show a 50% inhibition in concentrations between 5 - 30 µg/ml, which are within the range of antibiotic activity.

1

ANTI LEISHMANIA AND ANTI TRYPANOSOMA TESTS

A. Scoring of drug activity:

1. L. tropica

5

a. amastigotes in peritoneal exudate cells  
in Mc Coy's medium in vitro at 37° C.

+++ = clearance of all parasites in 24 hrs

++ = clearance of all parasites in 48 hrs

+ = clearance of all parasites in 72 hrs

10

+ = partial clearance of parasites in  
72 hours or more

- = no activity against parasites.

b. promastigotes in Mc Coy's medium in vitro  
at 27° C.

15

+++ = no viable parasites after 24 hours

++ = no viable parasites after 48 hours

+ = no viable parasites after 72 hours

+ = no viable parasites after 96 hours

- = viable parasites after 120 hours.

11. Trypanosoma in vitro

20

Trypanosoma in RPMI medium in vitro at 37° C.  
Scoring as in b.

1 ANTI LEISHMANIA AND ANTI TRYPANOSOMA TESTS

Results:

		Leishmania		Trypanosoma			
5	Compound or Ex.No.	Amastigote		Promastigote		in vitro	
		10µg	100µg	10µg	100µg	10 µg	100 µg
	1	+	+	-	+++*	+	+++**
	14	+	++			+++	+++*
	15			-	+++		
10	Control Pentamidine			+++	+++	-	++

\* An effect was observed with this drug after 1 h at this concentration. No effect was observed with Pentamidine at this time.

\*\* Slight effect.

15 Summary:

The tested compounds of Examples Nos. 1, 14, 15 were found to be active against Leishmania.

The tested compounds of Examples Nos. 1, 14 were found to be active against Trypanosoma.

1

ANTIPARKINSON ACTIVITY

Male Charles River albino rats, weighing 200-250 g, were used. Catalepsy was produced by haloperidol, 5 mg/kg i.p. The animals were placed with their front paws on a horizontal bar, about 10 cm above the ground, and animals were considered cataleptic if not changing posture for at least 30 sec. Cataleptic animals were injected l.p. with one of the drugs at a dose of 40-80 mg/kg. Catalepsy was estimated again at the intervals indicated.

Drug: Control Symmetrel, Route, i.P., Dose: 80 mg/kg

<u>Time</u>	<u>Rat 1</u>	<u>Rat 2</u>	<u>Rat 3</u>	<u>rat 4</u>	<u>rat 5</u>
0	+	+	+	+	+
45	+	-	-	-	-
90	+	-	+	+	-
110	+	+	-	-	-
180	+	+	-	-	+
anticataleptic effect	0/4	2/4	3/4	3/4	3/4
Mean maximal effect					2.2/4

1

ANTI PARKINSON  
EVALUATION OF ANTICATALEPTIC EFFECT IN RATS

5

10

Male Charles River albino rats, weighing 200-250 g, were used. Catalepsy was produced by haloperidol, 5 mg/kg i.p. The animals were placed with their front paws on a horizontal bar, about 10 cm above the ground, and animals were considered cataleptic if not changing posture for at least 30 sec. Cataleptic animals were injected i.p. with one of the drugs at a dose of 40-80 mg/kg. catalepsy was estimated again at the intervals indicated.

Drug: Compound of Example 7, Route: i.p., Dose: 80 mg/kg

	<u>Time</u>	<u>rat 1</u>	<u>rat 2</u>	<u>rat 3</u>	<u>rat 4</u>	<u>rat 5</u>
	0	+	+	+	+	+
15	45	-	+	+	+	+
	90	+	+	+	+	-
	110	+	+	+	+	-
	180	+	+	+	+	-
	Anticataleptic					
20	effect	1/4	0/4	0/4	0/4	3/4

mean maximal effect 0.8/4

1

STEREOTYPED BEHAVIOUR IN MICE

Male ICR albino mice weighing 25-30 g were put in cages with a metal grid floor, 4 in each cage. Drugs were injected intraperitoneally and stereotyped behaviour (sniffing, biting, repetitive head movement) was evaluated every 30 min.

5

Drug Control Symmetrel Route l.p. Dose 50 mg/kg

	<u>Time (min)</u>	<u>Mouse 1</u>	<u>Mouse 2</u>	<u>Mouse 3</u>	<u>Mouse 4</u>
10	0	0	0	0	0
	30	1	1	1	1
	45	1	1	1	1
	60	2	2	1	1
	90	1	1	2	1
15	120	2	2	2	2
	135	2	2	2	2
	150	2	2	2	2
	180	2	2	2	2
	210	2	2	2	1
20	240	2	2	2	0
Total					
Score		17	17	17	13

Mean Score 16

1 Drug Compound of Example 7 Route I.p. Dose 50 mg/kg

	<u>Time (min)</u>	<u>Mouse 1</u>	<u>Mouse 2</u>	<u>Mouse 3</u>	<u>Mouse 4</u>
	0	0	0	0	0
5	30	2	0	0	0
	45	2	0	1	0
	60	2	0	0	0
	90	2	2	0	0
	120	2	2	0	0
10	135	2	2	0	0
	150	2	2	1	0
	180	1	1	1	0
	210	1	1	2	2
	240	1	1	1	1
15	Total				
	Score	17	11	6	3

Mean Score 9.25

Summary:

20 The tested compound of Example 7 was found to be active.

1

ANTIMYCOTIC ACTIVITY

(Human)

The method for the evaluation was as follows:

Microorganisms:

5

1. *Candida albicans*
2. *Trichophyton rubrum*
3. *Trichophyton mentagrophytes*.

Assay:

10

Concentrations of 10 µg/ml, 50 µg/ml, 100 µg/ml, of each of the tested compounds were mixed in a Sabouraud dextrose agar, on which the test organisms were inoculated.

Evaluation:

15

Control (full growth): ++++  
No growth: -

The results are summarized in the following table:

1

ANTI HUMAN FUNGI AND YEAST

Compound of Example No.		Concent. µg/ml	C. albicans	T. rubrum	T. menta grophytes
5	Control	10	++++	++++	++++
		50	++++	++++	++++
		100	++++	++++	++++
10	1. 3	10	++++	+++	+++
		50	++++	++	++
		100	++++	+	++
10	2. 8	10	++++	++++	++++
		50	++++	++	++
		100	++++	±	±
15	3. 16	10	++++	++	+++
		50	++++	+	+
		100	+++	+	±
	4. 38	10	++++	++++	++++
		50	++++	++	±
		100	++++	++	±

Results:

- 20 The results indicate that the tested compounds of Examples 3, 8, 16, 38 demonstrate an activity in the range of 50 - 100 µg/ml.

1 INHIBITION TEST ON HSV REPLICATION

Cells - BSC-1 (Green monkey Kidney)  
 Virus - HSV-1 (Herpes Simplex)  
 Inoculum - 10 PFU/cell  
 5 Medium - DMEM + 10% C.S.

Herpes

J. Levitt & Y. Becker

Virology 31, 129-134 (1967)

10	Compound of Example No.	Concent $\mu\text{g/ml}$	T.L. $\mu\text{g/ml}$ *	% Inhibition **
			Toxic Limit	
	Ex.7	100	50	99.9
		75		98
		50		92
		25		72.5
15	Ex.31	100		97
		50		91
		25		51

\* T.L. The highest concentration of compound which is completely not toxic.

20 \*\* % Inhibition of control infected for some time with same virus PFV with no inhibition.

Results

The tested compounds of Examples 7, 31 were found to inhibit HSV by 96-99% at a concentration of 50-200  $\mu\text{g/ml}$ .

25 Anti-influenza virus effects (preliminary results)

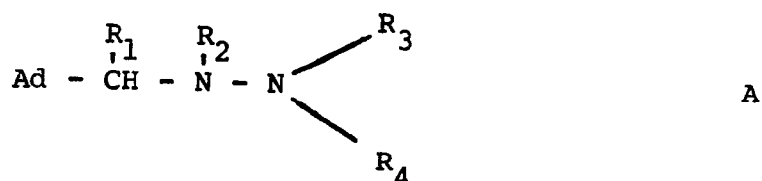
Method :

G. Appleyard and Maber J. of Gen. Virol. 25, 351-357 (1974).

30 The tested compounds of Examples 7, 31, 23, 29, 38, 41, 8 were found effective against influenza A virus at a concentration of 10-50  $\mu\text{g/ml}$ .

1 CLAIMS:

1. 1- or 2-Adamantylmethyl hydrazines of the general formula A



5 wherein Ad is 1- or 2-adamantyl, R<sub>1</sub> and R<sub>2</sub> are the same or different and are each hydrogen or a lower unsubstituted or substituted alkyl group of 1-4 carbon atoms; R<sub>3</sub> and R<sub>4</sub> are the same or different and are each hydrogen, an unsubstituted or substituted radical being a lower alkyl of 1-4 carbon atoms, a lower alkanolic acid radical of 2-4 carbon atoms or a lower alkyl ester thereof, adamantyl, aryl, aralkyl in which the alkyl moiety has 1-4 carbon atoms or an unsubstituted or substituted heterocyclic radical of aromatic character; or R<sub>3</sub> and R<sub>4</sub> together with the nitrogen atom to which they are attached form a cyclic radical; and pharmaceutically acceptable acid addition salts thereof.

20 2. 1-(Adamant-1'-ylmethyl)-2-methylhydrazine and pharmaceutically acceptable acid addition salts thereof.

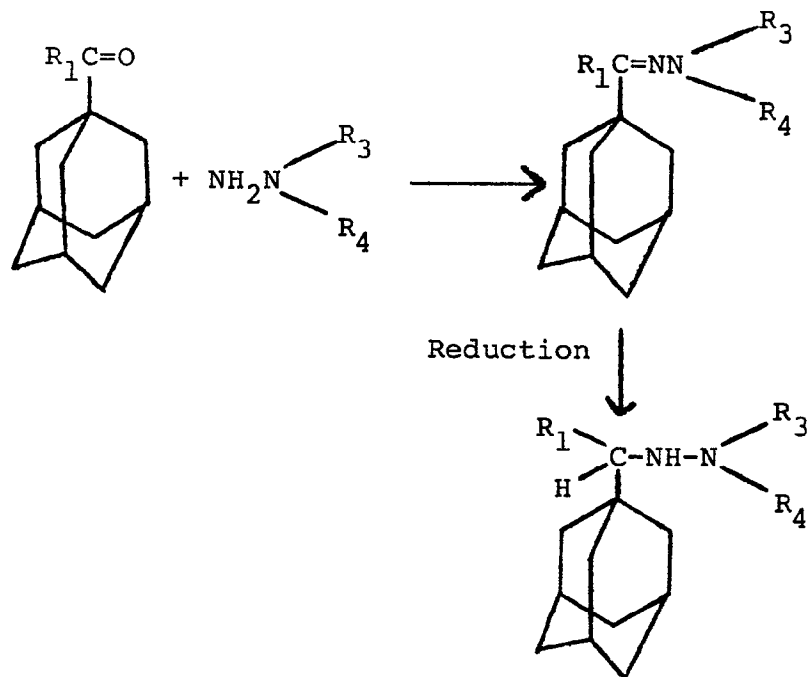
- 1           3.    1-(Adamant-1'-ylmethyl)-2,2-dimethyl-  
hydrazine and pharmaceutically acceptable acid addition  
salts thereof.
4.    1-(Adamant-1'-ylmethyl)-2-benzylhydrazine  
5   and pharmaceutically acceptable acid addition salts  
thereof.
5.    1-(Adamant-1'-ylmethyl)-2,2-diphenyl-  
hydrazine and pharmaceutically acceptable addition  
salts thereof.
- 10           6.    1-(Adamant-1'-ylmethyl)-2-(m-trifluoro-  
methylphenyl)hydrazine and pharmaceutically acceptable  
acid addition salts thereof.
7.    1-(Adamant-1'-ylmethyl)-2-(o-carboxyphenyl)-  
hydrazine and pharmaceutically acceptable acid addition  
15   salts thereof.
8.    1-(Adamant-1'-ylmethyldamino)pyrrolidine and  
pharmaceutically acceptable acid addition salts  
thereof.
9.    1-(Adamant-1'-ylmethyldamino)piperidine and  
20   pharmaceutically acceptable acid addition salts thereof.
10.   4-(Adamant-1'-ylmethyldamino)morpholine and  
pharmaceutically acceptable acid addition salts thereof.
11.   1-(Adamant-1'-ylmethyldamino)-4-methyl-  
piperazine and pharmaceutically acceptable acid  
25   addition salts thereof.
12.   1-(Adamant-1'-ylmethyldamino)-4-(m-trifluoro-  
methyl)piperazine and pharmaceutically acceptable acid  
addition salts thereof.

1 in which  $R_1$  is as in formula A, with a hydrazine  
compound in which at least one of the nitrogens does  
not bear any substituent to produce the corresponding  
hydrazone, and reducing the latter.

5 In the above process the reduction may be  
effected in any suitable conventional way, e.g. with  
a reducing agent such as sodium cyanoborohydride or  
by catalytic hydrogenation using any suitable  
conventional hydrogenation catalyst such as, for  
10 example, Adam's Catalyst.

The above embodiment for the preparation of  
compounds according to the invention is illustrated  
in the following Reaction Scheme I in which  $R_1$ ,  $R_3$   
and  $R_4$  have the same meanings as in formula A and  
15 the  $R_1C=O$  group is depicted in the 1-position:

Reaction Scheme I



- 1                   This general method was applied in  
accordance with the invention in the preparation of  
the following adamantylmethylhydrazine derivatives:
- 1-(Adamant-1'-ylmethyl)-2-methylhydrazine
- 5   1-(Adamant-1'-ylmethyl)-2,2-dimethylhydrazine  
1-(Adamant-1'-ylmethyl)-2-[1"-(2"-hydroxyethyl)]-  
hydrazine  
1-(Adamant-1'-ylmethyl)-2-benzylhydrazine  
1-(Adamant-1'-ylmethyl)-2-phenethylhydrazine
- 10   1-(Adamant-1'-ylmethyl)-2-(p-bromophenyl)hydrazine  
1-(Adamant-1'-ylmethyl)-2,2-diphenylhydrazine  
1-(Adamant-1'-ylmethyl)-2-(m-trifluoromethylphenyl)-  
hydrazine  
1-(Adamant-1'-ylmethyl)-2-(o-carboxyphenyl)hydrazine
- 15   1-(Adamant-1'-ylmethyl)-2-[4"-(7"-chloroquinolinyl)]-  
hydrazine  
1-(Adamant-1'-ylmethylamino)pyrrolidine  
1-(Adamant-1'-ylmethylamino)-2-methylpyrrolidine  
1-(Adamant-1'-ylmethylamino)piperidine
- 20   1-(Adamant-1'-ylmethylamino)homopiperidine  
1-(Adamant-1'-ylmethylamino)heptamethylamine  
4-(Adamant-1'-ylmethylamino)morpholine  
1-(Adamant-1'-ylmethylamino)-4-methylpiperazine  
1-(Adamant-1'-ylmethylamino)-4-(m-trifluoromethyl-
- 25   phenyl)piperazine  
1-(Adamant-2'-ylmethyl)-2,2-dimethylhydrazine  
1-(Adamant-2'-ylmethyl)-2-(pyrid-2"-yl)hydrazine  
1-(Adamant-2'-ylmethylamino)pyrrolidine  
1-(Adamant-2'-ylmethyl)-2-(1'-adamantyl)hydrazine
- 30   1-[ (Adamant-1'-yl)ethyl] hydrazine  
1-[1'-(Adamant-1"-yl)ethyl]-2-methylhydrazine  
1-[1'-(Adamant-1"-yl)ethyl]-2-(m-trifluoromethyl-  
phenyl)hydrazine

- 1                   32.    1-(Adamant-2'-ylmethylamino)-  
piperidine and pharmaceutically acceptable acid  
addition salts thereof.
- 5                   33.    1-(Adamant-2'-ylmethyl)-2-(1"-  
adamantyl)hydrazine and pharmaceutically acceptable  
acid addition salts thereof.
34.    1-(Adamant-1'-ylmethylamino)thio-  
morpholine and pharmaceutically acceptable acid  
addition salts thereof.
- 10                  35.    1-(Adamant-1'-ylmethylamino)hydantoin  
and pharmaceutically acceptable acid addition salts  
thereof.
36.    1-(Adamant-1'-ylmethyl)-2-butyl-  
hydrazine and pharmaceutically acceptable acid  
15 addition salts thereof.
37.     $\alpha$ -[2-(Adamant-1'-ylmethyl)hydrazino]-  
butanoic acid and pharmaceutically acceptable acid  
addition salts thereof.
- 20                  38.    1-(Adamant-1'-ylmethyl)-1-isopropyl-  
hydrazine and pharmaceutically acceptable acid addit-  
ion salts thereof.
39.    1-[(Adamant-1'-ylmethyl)methylamino]-  
pyrrolidine and pharmaceutically acceptable acid  
addition salts thereof.
- 25                  40.    1-(Adamant-1'-ylmethyl)-2-isopropyl-  
hydrazine and pharmaceutically acceptable acid  
addition salts thereof.

1           41.   1-(Adamant-1'-ylmethylamino)-3-  
          methylpyrrolidine and pharmaceutically acceptable acid  
          addition salts thereof.

          42.   A composition containing as active  
5   ingredient a compound according to Claim 1.



European Patent  
Office

# EUROPEAN SEARCH REPORT

0002065  
Application number  
EP 78 10 1411

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. <sup>2</sup> )
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	<u>FR - M - 818M</u> (BAYER) * Seiten 1,2 *  -----	1,42	A 61 K 31/15 C 07 C 109/00 109/04 C 07 D 295/22 213/77 215/42 233/80
			TECHNICAL FIELDS SEARCHED (Int. Cl. <sup>2</sup> )
			C 07 C 109/04 C 07 D 295/22 213/77 215/42 233/80
			CATEGORY OF CITED DOCUMENTS
			X: particularly relevant A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention E: conflicting application D: document cited in the application L: citation for other reasons
			&: member of the same patent family, corresponding document
<div><div><input checked="" type="checkbox"/></div><div>The present search report has been drawn up for all claims</div></div>			
Place of search Den Haag		Date of completion of the search 02-02-1979	Examiner FRANCOIS